

## Colistin and Polymyxin B in Critical Care

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During the last years, the emergence of gram-negative bacteria resistant to most available antibiotics all over the world has led to the readministration of polymyxins B and E as “salvage” therapy in critically ill patients [1]. The incidence of intensive care unit (ICU)-acquired infections caused by multidrug-resistant (MDR) gram-negative pathogens that may cause pneumonia/ventilator-associated pneumonia (VAP), bacteremia, meningitis, urinary tract infections, and central venous catheter-related infections has been on the increase worldwide in the past 10 years [2,3]. For this reason, old antibiotics, such as polymyxin E (colistin) or polymyxin B, have come back [4]. There have been many clinical reports on the successful use of colistin or polymyxin B against infections caused by MDR *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* strains. Studies investigating the minimum inhibitory concentrations (MICs) of polymyxins against these MDR pathogens indicate their activity.

### **Emergence of intensive care unit-acquired infections caused by multidrug-resistant gram-negative pathogens**

The emergence and rapid spread of MDR isolates, including *P aeruginosa*, *A baumannii*, *K pneumoniae*, and *Enterobacter* that cause ICU or

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nosocomial-acquired infections are of great concern worldwide [5–9]. These pathogens cause nosocomial infections and outbreaks, particularly among critically ill patients hospitalized in ICUs or burn units and immunocompromised patients [10]. The emergence of serious infections caused by MDR pathogens in critically ill patients poses a treatment challenge. Carbapenems, antibiotics of choice for these pathogens, are becoming gradually less useful in severely ill patients in whom outbreaks involving carbapenem-resistant *A baumannii*, *P aeruginosa*, *K pneumoniae*, and *Enterobacter aerogenes* sp have been described [11,12].

### History of polymyxins

Polymyxins, a group of cationic polypeptide antibiotics consisting of five different compounds (polymyxin A-E), were discovered in 1947 [13]. Colistin, also known as polymyxin E, was the first antibiotic discovered in Japan, in 1949 [14]. Only polymyxins B and E have been used in clinical practice. Polymyxin B differs by only one amino acid from colistin. Colistin and polymyxin B are produced from *Bacillus* spp [15].

Colistin was synthesized nonribosomally by *Bacillus polymyxa* subspecies colistinus [16]. It was first used in Japan and later in Europe during the 1950s and in the United States in 1959 [17]. The intravenous formulations of colistin and polymyxin B were used for approximately two decades but were gradually abandoned worldwide in the early 1970s because of the reported severe toxicities [18–24]. During the past two decades, intravenous administration of colistin was mainly restricted for the treatment of respiratory tract infections caused by MDR gram-negative pathogens in patients with cystic fibrosis [25–27]. On the other hand, polymyxins have been used worldwide in topical and ophthalmic solutions for decades.

In the recent literature, encouraging findings regarding the reuse of colistin for the treatment of infections caused by MDR pathogens such as *P aeruginosa* and *A baumannii* were first reported by Levin and colleagues [28], followed by other reports that confirmed the favorable results of this antibiotic [29]. Early therapy with inhaled colistimethate sodium (CMS), the prodrug of colistin, is being used with good effectiveness in preventing deterioration in patients who have cystic fibrosis and chronic infection. Several chronically infected patients who have cystic fibrosis also have been treated successfully with 3-month courses of intravenous CMS [30].

### Forms of colistin

Two forms of colistin are available commercially: CMS (also called sodium colistin methanesulphonate, colistin methanesulfonate, colistin sulfo-methate, or colistimethate), which is used for parenteral and inhalation therapy, and colistin sulfate, which is used orally and for topical use. Great

care is needed to avoid confusion between colistin (base) and CMS; it is essential not to use the terms interchangeably. It has been demonstrated recently that CMS is a prodrug of colistin [31].

Both preparations are hydrolysed to a complex mixture of partially sulphonated derivatives, which possess varying antibacterial activities, and colistin itself. Colistin and CMS have different structures; colistin is a polycation and CMS is a polyanion at physiologic pH [32]. Colistin is two- to fourfold more active against *P aeruginosa* than CMS. The presence of colistin in plasma from patients who have cystic fibrosis shortly after intravenous administration of CMS has been demonstrated, as has the rapid conversion of CMS to colistin after intravenous administration of CMS to rats [33]. It is presumed that plasma or serum samples contain many intermediate metabolites of CMS. The complex chemistry of CMS and the differences between CMS and colistin in terms of stability, pharmacokinetics, and pharmacodynamics have not been fully recognized [34].

### Mechanism of action

Polymyxins are a group of polypeptide cationic antibiotics that consist of a cyclic decapeptide molecule, positively charged and linked to a fatty acid chain that has been found to be either 6-methyl-octanoic acid or 6-methyl-heptanoic acid. The main difference between the molecules of polymyxin B and E is in the amino acid components [35]. The cationic molecules of polymyxin B and colistin compete and displace  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  ions, which normally stabilize the lipopolysaccharide molecule of the outer membrane of gram-negative bacteria. They are comprised of a polycationic peptide ring that contains ten amino acids and a fatty acid side chain. Both of these compounds are bactericidal, targeting the bacterial cell wall, disrupting membrane permeability, and ultimately leading to cell death.

The polymyxins exert their bactericidal activity by binding to the bacterial cell membrane and disrupting its permeability, which results in leakage of intracellular components. They also have antiendotoxin activity [36]. These agents are rapidly bactericidal against many gram-negative bacteria. The polymyxin antimicrobials are poorly absorbed from the gastrointestinal tract. Colistin concentrates in the liver, kidney, muscle, heart, and lungs but does not consistently cross the blood-brain barrier in noninflamed meninges. The poor dialyzability of the polymyxins may be caused by their large molecular size and not their plasma or tissue-binding ability [37]. Polymyxins are excreted primarily by the kidneys. Pharmacokinetic studies in the 1960s demonstrated that the serum half-life of these drugs increases from 6 hours or less in individuals with normal renal function to 48 hours or more in anuric patients [38,39].

Owen and colleagues [40] examined recently the in vitro pharmacodynamics of colistin against *A baumannii* clinical isolates. They found that

colistin showed rapid killing in a concentration-dependent manner. Colistin exhibited modest postantibiotic effect, however. Their results suggest that monotherapy with CMS, the parenteral form of colistin, and long dosage intervals (eg, 24 hours) may be problematic for treatment of infections caused by colistin-heteroresistant *A baumannii*, although these findings should be supplemented by clinical studies.

Colistin has good activity against *Acinetobacter* spp ( $\text{MIC}_{90} \leq 2 \text{ mg/L}$ ), *K pneumoniae* ( $\text{MIC}_{90} \leq 1 \text{ mg/L}$ ), *E coli* ( $\text{MIC}_{90} \leq 2 \text{ mg/L}$ ), *P aeruginosa* ( $\text{MIC}_{90} \leq 4 \text{ mg/L}$ ) [41], and *Enterobacter* spp ( $\text{MIC}_{50} \leq 1 \text{ mg/L}$ ). It also may be active against some strains of *Shigella* spp ( $\text{MIC}_{90} \leq 0.5 \text{ mg/L}$ ), *Salmonella* spp ( $\text{MIC}_{90} \leq 1 \text{ mg/L}$ ), *Citrobacter* spp ( $\text{MIC}_{90} \leq 1 \text{ mg/L}$ ), and *E coli* ( $\text{MIC}_{90} \leq 1 \text{ mg/L}$ ). No useful activity was demonstrated against *Providentia* spp or *Serratia* spp [42]. Colistin has a rapid concentration-dependent bactericidal activity at concentrations between 3 and 200 mg/L, although there is no clearly increased colistin activity at concentrations above 18 mg/L. Polymyxin B exhibits good activity against *P aeruginosa* at  $\text{MIC}_{90} \leq 4 \text{ mg/L}$  [43].

### Dosage of colistin and polymyxin B in critical care

Colistin dosing has ranged from 2.5 to 5.0 mg/kg/d in patients with normal renal function and is usually given two to four times a day [44]. In the United Kingdom, for adult patients and children older than 12 years who have normal renal function and body weight more than 60 kg, a dosing regimen of 240 to 480 mg (3–6 million IU) of CMS per day in three divided doses is recommended. In patients who have normal renal function and body weight 60 kg or less, 4 to 6 mg/kg (50,000–75,000 IU/kg) of CMS per day divided in three doses is recommended. It is remarkable that there is a substantial difference in the recommended doses of the European and US products. The recommended upper limit dosage for a 60-kg patient with normal renal function is 480 mg of CMS per day for the European product and approximately 800 mg of CMS per day for the US product [45]. Several clinical studies from Europe reported that in critically ill adult patients with normal renal function and body weight more than 60 kg, CMS was administered intravenously in a dose of 9 million IU divided into three equal doses.

The dosage of intravenous polymyxin B recommended by the manufacturer is 1.5 to 2.5 mg/kg/d (15,000–25,000 IU/kg/d) divided into two equal doses for adults and children older than 2 years with normal renal function. One milligram of polymyxin B is equal to 10,000 IU.

Dosage adjustments are recommended for patients with mild to moderate renal dysfunction. Specifically, when the serum creatinine level is 1.3 to 1.5 mg/dL, 1.6 to 2.5 mg/dL, or above 2.6 mg/dL, the recommended dosage of intravenous colistin for serious infections is 2 million IU every 12 hours,

24 hours, or 36 hours, respectively. For patients with renal failure that necessitates dialysis, the recommended intravenous dosages of CMS are 2 to 3 mg/kg after each hemodialysis treatment [46] and 2 mg/kg daily during peritoneal dialysis [47]. Recommendations for dosage adjustment of polymyxin B in the presence of renal impairment have not been well established.

It is remarkable to emphasize the existing confusion regarding the correct dosing of colistin worldwide. To avoid confusion regarding dosing of colistin, it is preferable to use a dosing system based on international units. The use of international units for colistin dosing helps decrease confusion related to various formulations of this regimen [48]. Pure colistin base has been assigned a potency of 30,000 IU/mg, whereas CMS has a potency of 12,500 IU/mg. It should be noted that the formulation manufactured by Alpharma A/S (Copenhagen, Denmark) and distributed by Forest Laboratories (Kent, United Kingdom) in Europe contains 80 mg of CMS (1 million IU).

So far, most investigations on the pharmacodynamics of the polymyxins have focused on colistin, and less is known about the pharmacodynamics of polymyxin B [49]. Better understanding of the pharmacodynamics of polymyxin B may help to determine its exact dose rationally to optimize patient outcomes and avoid resistance. Recently, Tam and colleagues [50] examined the pharmacodynamics of polymyxin B against *P aeruginosa* and suggested that the bactericidal activity of this regimen was concentration dependent and seemed to be related to the ratio of the area under the concentration-time curve to the MIC. Investigations for the determination of the optimal dosage of these regimens in different subpopulations of patients are urgently required, however.

### Administration of colistin and polymyxin B in critical care

The incidence of infections caused by pathogens resistant to  $\beta$ -lactam agents, cephalosporins, aminoglycosides, and quinolones has increased sharply in recent years. The prevalence of such resistant pathogens in ICUs is as high as 21.8% in large teaching hospitals [51]. They are associated with high mortality rates. For example, the mortality rates for *A baumannii* infections have been reported to be 52% for bacteremias and 23% to 73% for pneumonia [52].

Most of the reintroduction of polymyxins in critical care during the last few years is related to colistin. The polymyxins are active against selected gram-negative bacteria, including *Acinetobacter* sp, *P aeruginosa*, *Klebsiella* sp, and *Enterobacter* sp. These pathogens can cause a multitude of ICU-acquired infections, including pneumonia/VAP, bacteremia, meningitis, urinary tract infections, and skin and soft tissue infections. Isolates resistant to almost all commercially available antimicrobials have been identified, thus limiting treatment options. The development of new agents against MDR gram-negative bacteria and reappraisal of older compounds (ie, polymyxins) are necessary for the optimal treatment of these pathogens.

Polymyxins B and E were mainly administered for the treatment of life-threatening nosocomial acquired infections caused by MDR gram-negative pathogens in adult patients. However, there are recent reports on the intravenous administration of these agents in children [53].

### Administration of colistin in ventilator-associated pneumonia

Garnacho-Montero and colleagues [29] administered intravenous CMS in 21 of 35 patients with VAP caused by MDR *A baumannii* strains susceptible exclusively to colistin. The rest of patients ( $n = 14$ ) had similar APACHE II scores at the time of ICU admission and Sequential Organ Failure Assessment scores at time of VAP diagnosis and received meropenem based on sensitivity tests and MICs. The observed outcomes, including in-hospital mortality, VAP-related mortality, and clinical cure, were similar in the compared groups. VAP was considered clinically cured in 57% of cases in both groups.

We reported our experience with the management of ICU-acquired pneumonia, namely VAP, due to MDR gram-negative bacteria (*P aeruginosa* and *A baumannii*) in 45 patients who had no history of cystic fibrosis. All patients received intravenous CMS in combination with broad-spectrum antibiotics, such as carbapenems, piperacillin/tazobactam, and ampicillin/sulbactam. A subset of patients also received aerosolized CMS at a mean daily dosage of 3.2 million IU (256 mg) divided in three equal doses as an adjunctive to the intravenous treatment. The observed clinical cure was 30 of 45 patients (66.7%), and the survival rate was 75.6% [54].

In a prospective cohort study, Reina and colleagues [55] examined the safety and effectiveness of colistin in ICU-acquired infections caused by *A baumannii* and *P aeruginosa* in 185 ICU patients. Patients received colistin ( $n = 55$ ) or other antibiotics ( $n = 130$ ), mainly carbapenems (81%). The two groups were similar in age, APACHE II, medical status, and Sequential Organ Failure Assessment score. The most frequent infection was VAP: 53% in colistin versus 66% in noncolistin group. Clinical cure on ICU day 6 of treatment was observed in 15% of colistin group and in 17% of noncolistin group. The mortality rates were 29% and 24%, respectively ( $P = \text{NS}$ ).

In a retrospective cohort study we also evaluated the effectiveness and nephrotoxicity of intravenous colistin monotherapy versus intravenous colistin/ $\beta$ -lactam combination in a group of patients with MDR gram-negative bacterial infections. Fourteen patients received colistin monotherapy and 57 received colistin/meropenem. The groups were similar in terms of demographics and comorbidity. Most patients suffered from pneumonia/VAP. No statistically significant differences were found regarding clinical response (cure and improvement) of the infection (12/14 [85.7%] versus 39/57 [68.4%],  $P = .32$ ) and development of nephrotoxicity (0/14 [0%] versus 4/57 [7%],  $P = .32$ ) between these two groups of patients. A favorable

association was revealed between survival and treatment with colistin monotherapy compared with colistin/meropenem (0/14 [0%] versus 21/57 [36.8%],  $P = .007$ ), even after adjusting for the variables for which statistically significant differences between the compared groups were found [56]. Further studies are needed to clarify the role of colistin monotherapy versus combinations of colistin with various antibiotics.

It should be mentioned that colistin should be used with caution to help preserve its activity as long as possible. It is interesting that the finding that prolonged use of combination of carbapenems ( $> 20$  days) and colistin ( $> 13$  days) was an independent predictor for pandrug-resistant *P aeruginosa* VAP [57].

### Administration of colistin in bacteremia/sepsis

Markou and colleagues [58] used 26 courses of intravenous colistin in 24 ICU patients with sepsis. Clinical response was observed for 73% of the treatments. Deterioration of renal function was found in 14.3% of patients, whereas survival at 30 days was 57.7%. Karabinis and colleagues [59] reported the successful management of a patient with bacteremia/septic shock caused by *K pneumoniae* in whom they administered colistin intravenously in a dosage of 9 million IU/d (2.5 mg/kg, divided into three doses). We used continuous intravenous colistin in a critically ill patient with bacteremia caused by a multiresistant *A baumannii* strain susceptible only to colistin; this approach led to the cure of this life-threatening infection [60].

Recently, we reported that the mortality rate was acceptable (35.7%) in critically ill patients with ICU-acquired bacteremia caused by MDR *A baumannii* who received intravenously colistin and meropenem, based on sensitivity tests and MICs. On the contrary, the mortality rate was 56% in the group of patients with bacteremia caused by *A baumannii* strains susceptible only to colistin [61].

### Administration of colistin in meningitis

Berlana and colleagues [62] administered colistin (intravenously, intramuscularly, inhaled, or intrathecally) in 80 patients infected with MDR *A baumannii* (86%) or *P aeruginosa* (14%). In 41 patients (51%), the episodes were caused by *A baumannii* strains susceptible exclusively to colistin. The causative organisms were cleared in 92% of the patients from whom post-treatment repeat specimens were obtained. The in-hospital mortality rate was 18% (14 patients).

A systematic review of the literature showed recently that 64 episodes of gram-negative meningitis (34 in adults) were treated with a combination of systemic and local polymyxins (25 episodes) or with polymyxin monotherapy via the intraventricular or intrathecal route (11 episodes). Cure was



achieved in 51 of 64 episodes (80%), 26 of 30 episodes (87%) caused by *P. aeruginosa*, and in 10 of 11 episodes (91%) caused by *Acinetobacter* spp. Toxicity related to local administration of polymyxins was noted in 17 of 60 (28%) patients. The most common complication was meningeal irritation (12 cases). Discontinuation of treatment was necessary in four episodes and dose reduction in four episodes; irreversible toxicity was not reported [63].

### Routes of administration

Another point of interest is that routes of colistin administration other than the intravenous one may have clinical value, including aerosolized (nebulized) administration of the antibiotic to patients with severe pneumonia or VAP. The value of aerosolized colistin in the prevention and treatment of infections caused by *P. aeruginosa* strains already has been proved for patients with cystic fibrosis [64].

Inhaled CMS or polymyxin B has been used in combination with conventional intravenous antibiotic treatment in critically ill patients with VAP caused by MDR gram-negative pathogens [65,66]. Although the number of patients receiving aerosolized colistin so far is limited, it was thought that this supplementary therapy is associated with improved outcome, suggesting that this approach merits further evaluation. The recommended dosage of nebulized CMS for adults is 2 to 4 million IU/d usually divided into three or four equal doses [67–69].

Intraventricular or intrathecal administration of colistin may prove to be a life-saving intervention for patients with meningitis caused by MDR gram-negative pathogen not responding to intravenous treatment with antimicrobial agents, including colistin. Several case reports in the literature indicate the success of this approach [70–73]. The recommended dosages in this case range from 3.75 mg to 10 mg CMS per day [74,75]. Some patients received intraventricular or intrathecal CMS treatment at a dose of 10 to 20 mg/d for a mean of 20 days, without presenting any adverse events. Direct instillation of colistin into the central nervous system may cause chemical meningitis or ventriculitis [76]. Issues such as dose and duration of treatment remain unresolved and require further evaluation in prospective controlled trials.

### Adverse events of polymyxin B and colistin

The major adverse events of polymyxins are nephrotoxicity, neurotoxicity, and neuromuscular blockade. Polymyxins can cause a direct toxic effect in kidneys that results in acute tubular necrosis and renal insufficiency or failure, manifested by increase in serum urea and creatinine levels associated



with decrease in creatinine clearance. Administration of polymyxins also can cause hematuria, proteinuria, and cylindruria. Nephrotoxicity of CMS seems to be less compared with that associated with polymyxin B. Concomitant administration of other potential nephrotoxic agents increases the likelihood for development of acute renal failure. When the administration of a polymyxin is associated with renal dysfunction, early discontinuation of this regimen is necessary. Appropriate fluid management to maintain a reasonable central venous pressure value, close monitoring of serum electrolytes, and quick diuresis by administration of mannitol (resulting in renal clearance of all nephrotoxic drugs) are necessary [77].

We recently prospectively evaluated the nephrotoxicity associated with the intravenous administration of colistin in 21 patients for at least 7 days. The mean daily dose of colistin was 5.5 million IU, whereas the mean duration of treatment was 15 days (range 7–54 days). Only 3 of 21 patients (14.3%) developed nephrotoxicity during treatment with CMS [78]. We also examined the toxicity of colistin after 19 courses of prolonged (defined as > 4 weeks) intravenous administration in 17 ICU patients. Mean daily dosage was 4.4 million IU, and mean duration of administration was 43.4 days. Median serum creatinine value increased by 0.25 mg/dL during the treatment period compared with baseline ( $P < .001$ ). No apnea or other evidence of neuromuscular blockade was noted in this group of patients [79].

The neurotoxic effects include oral and perioral paresthesia, headache, ataxia, vertigo, visual disturbances, confusion, lower limb weakness, and vasomotor instability [17]. These agents also can cause a reversible neuromuscular blockade leading to respiratory failure. Between 1964 and 1973, there are at least eight case reports in the literature correlating the intramuscular administration of polymyxins with development of episodes of respiratory apnea [80,81]. It is remarkable that all recently performed studies in critically ill patients with nosocomial-acquired infections caused by MDR gram-negative pathogens who received large doses of colistin did not report serious neurotoxicity correlated with the administration of this regimen. We could not identify reports in the literature over the past 15 years or more regarding episodes of neuromuscular blockade or apnea induced by polymyxins.

Other rare complications related to polymyxin administration are allergic reactions (contact dermatitis, itching, and rash), ototoxicity, drug fever, and gastrointestinal disturbances [82]. Complications related to administration of aerosolized colistin are sore throat, cough, bronchoconstriction even in patients with no history of bronchial asthma or atopy (due to chemical stimulation, liberation of histamine, allergy in the airways, irritation from chemicals the foam that is produced during nebulization, and hyperosmolarity in the airway), and chest tightness [83]. Bronchoconstriction usually requires discontinuation of the medication and administration of bronchodilators. It should be emphasized that solutions of colistin made for aerosolized treatment should be administered immediately after their preparation.

### Administration of polymyxin B in intensive care unit setting

Sobieszczyk and colleagues [84] examined retrospectively the clinical and microbiologic efficacy and safety profile of polymyxin B in the treatment of MDR gram-negative bacterial infections of the respiratory tract. Twenty-five critically ill patients received a total of 29 courses of polymyxin B administered in combination with another antimicrobial agent. Patients were treated with intravenous and aerosolized polymyxin B. Mean duration of polymyxin B therapy was 19 days (range 2–57 days). End of treatment mortality was 21%, and overall mortality at discharge was 48%. Nephrotoxicity was observed in three patients (10%) and did not result in discontinuation of therapy. The authors concluded that polymyxin B in combination with other antimicrobials can be considered a reasonable and safe treatment option for MDR gram-negative respiratory tract infections in the setting of limited therapeutic options. Similar good results were reported by Holloway and colleagues [85] after administration of intravenous polymyxin B in 29 critically ill patients with infections caused by MDR *A baumannii*. The observed clinical cure was 76%, whereas crude mortality rate was 27%.

Sarria and colleagues [86] reported their experience from the use of intravenous polymyxin B in a patient with *A baumannii* sepsis and acute renal failure that required continuous venovenous hemodialysis. The patient was treated successfully with intravenous polymyxin B.

### Summary

Recent studies in critically ill patients who received intravenous polymyxins for the treatment of serious *P aeruginosa* and *A baumannii* infections of various types, including pneumonia, bacteremia, and urinary tract infections, have led to the conclusion that these antibiotics have acceptable effectiveness and considerably less toxicity than was reported in old studies. The frequency of nephrotoxicity and severity of neurotoxicity seem to be substantially less than previously believed. Recently, a significant increase in the data gathered on colistin has focused on its chemistry, antibacterial activity, mechanism of action and resistance, pharmacokinetics, pharmacodynamics, and new clinical application. Colistin has attracted more interest during the last years because of its significant activity against MDR *P aeruginosa*, *A baumannii*, and *K pneumoniae* strains responsible for ICU-acquired infections in critically ill patients. It is likely that colistin will be an important antimicrobial option against MDR gram-negative bacteria for at least several years [32]. It should be mentioned that no well-designed, randomized controlled studies have been conducted to evaluate the effectiveness and safety of polymyxins for the treatment of life-threatening, ICU-acquired infections caused by MDR gram-negative pathogens, such as *P aeruginosa*, *A baumannii*, and *K pneumoniae*. For this reason, such trials are urgently needed.

It is worth noting that the selective pressure caused by extensive or inadequate colistin use may have contributed to the emergence of colistin resistance among *P aeruginosa*, *A baumannii*, and *K pneumoniae* isolates, potentially increasing morbidity and mortality rates in critically ill patients and necessitating prudent use of colistin [87]. For this reason, the empiric use of colistin should be limited to institutions in which there is recognized infection caused by MDR gram-negative bacilli [88].

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